Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

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Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 1 of 14) (Last updated May 7, 2013; last reviewed May 7, 2013)

This table provides clinicians with information regarding known or suspected pharmacokinetic interactions between drugs commonly used for treatment or prevention of HIV-associated opportunistic infections or for treatment of HIV infection. Note that there may be substantial inter-patient variability in the magnitude of the interactions. Moreover, the table only provides suspected interactions between 2 drugs when used in combination, but cannot be used to predict the interaction potential when three or more drugs with similar metabolic pathways are co-administered. In these cases, alternative options with less drug interaction potential or therapeutic drug monitoring (if available), should be considered.

Throughout the table, two recommendations are commonly used when concomitant administration of two drugs may lead to untoward consequences. The definitions for these terms used in the Recommendations column are summarized below:

Co-administration should be avoided.

Indicates there is strong evidence or likelihood that the drug-drug interaction will result in either

1) Markedly decreased concentrations of one or both drugs, which may render one or both drugs ineffective, or

2) Increased concentrations of one or both drugs, which may result in excessive risk of toxicity that cannot be managed with a dose modification of one or both drugs.

Co-administration should be avoided if possible.

There is a potential for significant pharmacokinetic interactions. However, co-administration of the drugs may be necessary if there are no other reasonable options that provide a more favorable risk-benefit assessment. In some instances, a suggested strategy is provided with the recommendation based upon available knowledge and alternatives. If other more favorable options exist, the clinician is advised to consider changing components of the regimen to accommodate a more effective and/or safer regimen.

Drug	Interacting With	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Artemether-Lumefantrine	Darunavir/ritonavir	Artemether AUC ↓ 16%; DHA AUC ↓ 18%; lumefantrine AUC ↑ 2.5-fold	Clinical significance unknown. Monitor for anti-malarial efficacy and lumefantrine toxicities.
	Efavirenz	Artemether AUC ↓ 79%; DHA AUC ↓ 75%; lumefantrine AUC ↓ 56%	Clinical significance unknown. If used, monitor closely for anti-malarial efficacy.
	Etravirine	Artemether AUC ↓ 38%; DHA AUC ↓ 15%; lumefantrine AUC ↓ 13%	Clinical significance unknown. If used, monitor closely for anti-malarial efficacy.
	Lopinavir/ritonavir	Artemether AUC ↓ 40%; DHA AUC ↓ 17%; lumefantrine AUC ↑ 470%	Data based on single dose study. Clinical significance unknown. Monitor for anti-malarial efficacy and lumefantrine toxicities.
	Nevirapine	Artemether AUC ↓ 72%; DHA AUC ↓ 37%; lumefantrine (no difference in one study, but AUC ↑ 55.6% in another study)	Clinical significance unknown. Monitor for anti-malarial efficacy.
	Rifampin	Artemether AUC ↓ 89%; DHA AUC ↓ 85%; lumefantrine AUC ↓ 68%	Co-administration should be avoided.
Atovaquone	Atazanavir/ritonavir	Atovaquone AUC ↓ 46%; no data with unboosted atazanavir (based on a single-dose PK study using atovaquone 250 mg/proguanil 100 mg fixed-dose combination tablet; no interaction data between boosted or unboosted atazanavir and atovaquone suspension)	Dose adjustment not established; if co-administered, monitor for decreased atovaquone efficacy.

Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 2 of 14)

Drug	Interacting With	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Atovaquone, continued	Doxycycline	Atovaquone concentrations ↓ 40% with tetracycline; interaction study with doxycycline not available	Dose adjustment not established; if co-administered, monitor for decreased atovaquone efficacy.
	Efavirenz	Atovaquone AUC ↓ 75% (based on a single-dose PK study using atovaquone 250 mg/proguanil 100 mg fixed-dose combination tablet; no interaction data between efavirenz and atovaquone suspension)	Co-administration should be avoided if possible. If co-administered, monitor for decreased atovaquone efficacy.
	Lopinavir/ritonavir	Atovaquone AUC ↓ 74% (based on a single-dose PK study using atovaquone 250 mg/proguanil 100 mg fixed-dose combination tablet; no interaction data between lopinavir/ritonavir and atovaquone suspension)	Co-administration should be avoided if possible. If co-administered, monitor for decreased atovaquone efficacy.
	Rifabutin	Atovaquone AUC ↓ 34%; rifabutin AUC ↓ 19%	Dose adjustment not established; if co-administered, monitor for decreased atovaquone efficacy.
	Rifampin	Atovaquone concentrations ↓ 52%; rifampin concentrations ↑ 37%	Co-administration should be avoided.
	Zidovudine	Zidovudine AUC ↑ 31%	No dose adjustment necessary; monitor for zidovudine-associated toxicities.
Boceprevir	Atazanavir/ritonavir	Boceprevir AUC no change; atazanavir AUC ↓ 35%, C_{min} ↓ 49%; ritonavir AUC ↓ 36%	Co-administration should be avoided.
	Clarithromycin	May ↑ concentrations of clarithromycin	No dose adjustment necessary in patients with normal renal function. To avoid drug interaction, consider switching to azithromycin.
	Darunavir/ritonavir	Boceprevir AUC ↓ 32%, C_{min} ↓ 35%; darunavir AUC ↓ 44%, C_{min} ↓ 59%; ritonavir AUC ↓ 27%	Co-administration should be avoided.
	Efavirenz	Boceprevir AUC ↓ 19%, C_{min} ↓ 44%; efavirenz AUC ↑ 20%	Significance unknown; co-administration should be avoided.
	Elvitegravir/cobicistat/ tenofovir/emtricitabine	No PK data, bi-directional interaction possible	Co-administration should be avoided.
	Etravirine	Boceprevir AUC ↑ 10%, C_{min} ↓12%; etravirine AUC ↓ 23%, C_{min} ↓ 29%	Clinical significance of this interaction is unknown.
	Itraconazole, ketoconazole, posaconazole, voriconazole	Boceprevir AUC ↑ 230% when co-administered with ketoconazole 400 mg bid. Concentrations of azoles may be ↑	Doses of ketoconazole and itraconazole should not exceed 200 mg/day. Consider monitoring azole drug concentrations and adjust dose accordingly. Monitor for boceprevir-associated toxicities.

Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 3 of 14)

Drug	Interacting With	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Boceprevir, continued	Lopinavir/ritonavir	Boceprevir AUC ↓ 45%, C_{min} ↓ 57%; lopinavir AUC ↓ 34%, C_{min} ↓ 43%; ritonavir AUC ↓ 22%	Co-administration should be avoided.
	Raltegravir	No significant interaction.	This combination can be co-administered without dosage adjustment
	Rifabutin	↑ in rifabutin concentrations are anticipated, while exposure of boceprevir may be ↓	Co-administration should be avoided, if possible. If used in combination, consider monitoring rifabutin concentration and adjust dose accordingly.
	Rifampin	No PK data. Significant ↓ in boceprevir exposure is anticipated.	Co-administration should be avoided.
Caspofungin	Efavirenz, nevirapine	Possible ↓ in caspofungin concentrations based on regression analyses of patient PK data. No formal PK study available.	Manufacturer recommends consider increasing maintenance dose of caspofungin to 70 mg/day when co-administered with CYP450 inducers.
	Rifampin	Caspofungin C_{min} ↓ 30%	Caspofungin dose should be increased to 70 mg/day.
Clarithromycin	Atazanavir	Atazanavir C_{min} ↑ 91%, AUC ↑ 28%; clarithromycin AUC ↑ 94%, C_{min} ↑ 160% Co-administration with atazanavir/ritonavir has not been studied.	Because of concerns for QTc prolongation when these drugs are used in combination, reduce clarithromycin dose by 50% or switch to azithromycin.
	Boceprevir	Concentrations of clarithromycin may be ↑	No dose adjustment in patients with normal renal function. To avoid drug interaction, consider switching to azithromycin.
	Darunavir/ritonavir	Clarithromycin AUC ↑ 57%, C_{min} ↑ 174%	No dose adjustment in patients with normal renal function. To avoid drug interaction, consider switching to azithromycin.
	Efavirenz	Clarithromycin AUC ↓ 39%	Significance unknown; consider switching to azithromycin.
	Elvitegravir/cobicistat/ tenofovir/emtricitabine	Clarithromycin, cobicistat, and elvitegravir concentrations may be increased.	CrCl > 60 mL/min: no dosage adjustment. CrCl 50–60 mL/min: reduce clarithromycin dose by 50%. To avoid drug interaction, consider switching to azithromycin.
	Etravirine	Clarithromycin AUC ↓ 39%; etravirine C_{min} ↑ 46%, AUC ↑ 42%	Significance unknown; consider switching to azithromycin.

Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 4 of 14)

Drug	Interacting With	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Clarithromycin, continued	Fluconazole	Clarithromycin AUC ↑ 18%, C_{min} ↑ 33%	No dose adjustment necessary in patients with normal renal function.
	Itraconazole	Possible bi-directional CYP3A4 inhibition and increased exposure of both drugs.	Monitor for toxicities of both itraconazole and clarithromycin, consider monitoring drug concentrations and adjust dose accordingly, or consider switching to azithromycin.
	Lopinavir/ritonavir	Increased clarithromycin exposure expected.	No dose adjustment necessary in patients with normal renal function. To avoid drug interaction, consider switching to azithromycin.
	Maraviroc	Potential for inhibition of maraviroc metabolism and ↑ maraviroc concentration.	Decrease maraviroc dose to 150 mg BID or switch to azithromycin.
	Nevirapine	Clarithromycin AUC ↓ 29%, C_{min} ↓ 46%	Co-administration should be avoided if possible; consider switching to azithromycin.
	Rifabutin	Clarithromycin AUC ↓ by 44%; rifabutin AUC ↑ 76%–99%.	Consider reducing rifabutin dose, monitor for rifabutin-associated toxicities, Consider monitoring serum concentration and adjust dose accordingly; or switch to azithromycin.
	Rifampin	Mean clarithromycin concentration ↓ 87%	This combination should be avoided. Switch to azithromycin.
	Saquinavir	Saquinavir C_{max} ↑ 187%, AUC ↑ 177%; clarithromycin C_{max} and AUC ↑ 40% (studied with saquinavir 1200 mg TID) Clarithromycin has not been studied with ritonavir-boosted saquinavir.	No dose adjustment necessary in patients with normal renal function. Clarithromycin dose adjustment may be necessary in patients with renal dysfunction. Monitor closely because of additive risk of QTc prolongation associated with increased concentrations of both drugs. Consider switching to azithromycin.
	Telaprevir	Concentrations of both telaprevir and clarithromycin may be increased during co-administration.	Use with caution and monitor for adverse events, including QT prolongation. Reduce clarithromycin dose during concomitant use with telaprevir in patients with impaired renal function. Consider switching to azithromycin.

Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 5 of 14)

Drug	Interacting With	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Clarithromycin, continued	Tipranavir/ritonavir	Clarithromycin AUC ↑ 19%, C_{min} ↑ 68%; tipranavir AUC ↑ 66%, C_{min} ↑ 100%	Monitor for tipranavir-associated toxicities. No dose adjustment necessary in patients with normal renal function. Clarithromycin dose adjustment may be necessary in patients with renal dysfunction. Consider switching to azithromycin.
Dapsone	Rifampin	Dapsone concentrations ↓ 7 to 10-fold and half-life ($t_{1/2}$) ↓ from 24 to 11 hours.	Co-administration should be avoided if possible. Consider alternatives for dapsone or use rifabutin.
Doxycycline	Atovaquone	Atovaquone concentrations ↓ by approximately 40% with tetracycline; interaction study with doxycycline not available.	Until doxycycline-atovaquone interaction data become available, avoid this combination if possible.
	Rifampin	Doxycycline AUC ↓ by 59%	Potential for decreased doxycycline efficacy; monitor closely for therapeutic failure.
Erythromycin	Itraconazole	Itraconazole C_{max} ↑ 44%, AUC ↑ 36%. Potential for ↑ in erythromycin concentration.	Monitor for toxicities of both drugs, potential for QT prolongation; monitor itraconazole concentrations and adjust dose accordingly, or consider alternative azole or macrolide.
	Telaprevir	Concentrations of telaprevir and erythromycin may ↑ during co-administration.	Use with caution and monitor for adverse events, including QT prolongation.
Fluconazole	Clarithromycin	Clarithromycin AUC ↑ 18%, C_{min} ↑ 33%	No dose adjustment necessary in patients with normal renal function.
	Efavirenz	Efavirenz AUC ↑ 16%; no change in fluconazole AUC.	No dose adjustment necessary.
	Etravirine	Etravirine AUC ↑ 86%, C_{min} ↑ 109%	Co-administer with caution. Monitor for etravirine-associated toxicities.
	Nevirapine	Nevirapine concentrations ↑ 100% (compared with historic control).	Co-administration should be avoided, if possible. If co-administered, monitor for nevirapine-associated toxicities.
	Rifabutin	Rifabutin AUC ↑ 80%; no effect on fluconazole exposure.	Monitor for rifabutin-associated toxicities; consider monitoring rifabutin concentrations; may need to reduce rifabutin dose to 150 mg/day.
	Rifampin	Fluconazole AUC ↓ 23%–56%; no change in rifampin exposure.	Monitor for antifungal efficacy; may need to increase fluconazole dose.

Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 6 of 14)

Drug	Interacting With	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Fluconazole, continued	Saquinavir	Saquinavir C_{max} ↑ 56%, AUC ↑ 50% (studied with saquinavir 1200 mg TID). Fluconazole has not been studied with ritonavir-boosted saquinavir.	Significance unknown. No dosage adjustment needed.
	Tipranavir/ritonavir	Tipranavir AUC ↑ 50%, C_{min} ↑ 69%	Monitor for tipranavir-associated toxicities; fluconazole doses >200 mg/day not recommended.
	Zidovudine	Fluconazole ↓ glucuronidation of zidovudine; fluconazole 400 mg/day results in zidovudine AUC ↑ 74%	Monitor for zidovudine-associated toxicities.
Itraconazole	Boceprevir	Concentrations of itraconazole and/or boceprevir may be ↑	Itraconazole dose should not exceed 200 mg/day. Monitor itraconazole concentration and adjust dose accordingly.
	Clarithromycin	Possible bi-directional CYP3A4 inhibition and ↑ exposure of both drugs.	Monitor for toxicities of both itraconazole and clarithromycin. Monitor itraconazole concentration and adjust dose accordingly. Alternatively, consider switching to azithromycin.
	Efavirenz	Itraconazole AUC ↓ 39%, C_{min} ↓ 44% in PK studies; No change to efavirenz AUC. Failure to achieve therapeutic itraconazole concentrations has been reported.	Co-administration should be avoided if possible. If used in combination, monitor itraconazole concentrations and adjust dose accordingly.
	Elvitegravir/cobicistat/ tenofovir/emtricitabine	Cobicistat, elvitegravir, and itraconazole serum concentration may be ↑	Avoid itraconazole >200 mg/day. Monitor itraconazole serum concentrations with co-administration.
	Erythromycin	Potential for bi-directional inhibition of metabolism and ↑ serum concentrations of both drugs.	Monitor for toxicities of both drugs, potential for QT prolongation; monitor itraconazole concentrations and adjust dose accordingly, or consider alternative azole or macrolide.
	Etravirine	Etravirine concentration may be ↑; Itraconazole concentration may be ↓. Extent of the interaction unknown.	Dose adjustment with itraconazole may be necessary depending on the presence of other concomitant ARV drugs (e.g., PIs). Monitor itraconazole concentrations and adjust dose accordingly.
	Maraviroc	Potential for inhibition of maraviroc metabolism and ↑ in maraviroc concentration.	Decrease maraviroc dose to 150 mg twice daily.
	Micafungin	Itraconazole AUC ↑ 22%	No dose adjustment necessary.
	Nevirapine	Itraconazole C_{max} ↓ 38%, AUC ↓ 61%; nevirapine: no change	Monitor itraconazole concentrations and adjust accordingly dose; monitor therapeutic efficacy.

Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 7 of 14)

Drug	Interacting With	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Itraconazole, continued	PIs	Potential for bi-directional CYP3A4 inhibition with ↑ exposure of both drugs.	Monitor for PI-associated toxicities; monitor itraconazole concentrations and itraconazole-associated toxicities
	Rifabutin	Itraconazole AUC ↓ 70%; potential for inhibition of rifabutin metabolism and ↑ rifabutin exposure.	Co-administration should be avoided, if possible. If the combination is to be used, monitor itraconazole concentrations and adjust dose accordingly; monitor for rifabutin-associated toxicities and consider monitoring rifabutin concentrations.
	Rifampin	Itraconazole AUC ↓ 64%–88%; no change in rifampin concentrations.	Co-administration should be avoided. Consider alternative antifungal and/or antimycobacterial agent(s).
	Rilpivirine	Potential ↑ in rilpivirine exposure or ↓ in itraconazole.	No dose adjustment for rilpivirine; monitor for rilpivirine-associated toxicities. Consider monitoring itraconazole concentration and adjust dose as necessary.
	Telaprevir	Concentrations of itraconazole and telaprevir may be ↑	If co-administration is necessary, high doses of itraconazole (>200 mg/day) are not recommended. Monitor for toxicities to both drugs. Consider monitoring itraconazole concentration and adjust dose accordingly.
Mefloquine	Rifampin	Mefloquine AUC ↓ 68%.	Co-administration should be avoided, if possible. Use alternative anti-malarial drug or rifabutin.
	Ritonavir	When studied with ritonavir 200 mg twice daily—ritonavir AUC ↓ 31%, C_{min} ↓ 43%; no substantial change in mefloquine PK. Effect on exposure of ritonavir-boosted PIs unknown.	Use mefloquine with caution with PIs.
Micafungin	Itraconazole	Itraconazole AUC ↑ 22%	No dose adjustment necessary.
Posaconazole	Atazanavir (+/- ritonavir)	With unboosted-atazanavir—atazanavir AUC ↑ 268%; with ritonavir-boosted atazanavir—atazanavir AUC ↑ 146%	Co-administration should be avoided, if possible; or monitor atazanavir concentrations and adjust doses accordingly; monitor for atazanavir-associated toxicities.
	Boceprevir	Posaconazole concentration may be ↑	Use with caution, considering monitoring posaconazole concentration and adjust dose accordingly.

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Drug	Interacting With	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Posaconazole, continued	Efavirenz	Posaconazole AUC ↓ 50%, C_{max} ↓ 45%	Co-administration should be avoided, if possible; or monitor posaconazole concentrations and adjust doses accordingly.
	Elvitegravir/cobicistat/ tenofovir/emtricitabine	Cobicistat, elvitegravir, and posaconazole concentrations may be ↑	Monitor posaconazole concentration and adjust dose accordingly.
	Etravirine	Etravirine exposure may be ↑; posaconazole exposure unlikely to be affected.	No dose adjustment necessary; monitor for etravirine-associated toxicities.
	Fosamprenavir	Amprenavir AUC ↓ 65%; posaconazole AUC ↓ 23% (studied without ritonavir boosting). No data for fosamprenavir/ritonavir.	Co-administration should be avoided, or monitor drug concentrations and adjust doses accordingly.
	Rifabutin	Posaconazole AUC ↓ 49%; rifabutin AUC ↑ 72%.	Co-administration should be avoided, if possible, or monitor posaconazole and rifabutin concentrations and adjust doses accordingly; monitor clinical response.
	Rifampin	Posaconazole exposure may be ↓ significantly.	Co-administration should be avoided, if possible. If used, monitor posaconazole concentrations and adjust dose accordingly.
	Rilpivirine	Potential ↑ in rilpivirine concentrations.	Monitor for rilpivirine-associated toxicities.
	Ritonavir	Ritonavir AUC ↑ 80%, C_{max} ↑ 49%	No ritonavir dose adjustment necessary.
	Telaprevir	Concentrations of posaconazole and telaprevir may be ↑	Use with caution with increased monitoring for posaconazole- or telaprevir-associated toxicities, including QT prolongation. Consider monitoring posaconazole level and adjust dose accordingly.
Proguanil	Atazanavir/ritonavir	Proguanil AUC ↓ 41%; no data with unboosted atazanavir.	Use with caution.
	Efavirenz	Proguanil AUC ↓ 43%	Use with caution.
	Lopinavir/ritonavir	Proguanil AUC ↓ 38%	Use with caution.
Ribavirin	Didanosine	↑ intracellular concentrations of ddA-TP	↑ serious didanosine-associated mitochondrial toxicities. Co-administration should be avoided.

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Drug	Interacting With	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Rifabutin	Atovaquone	Atovaquone AUC ↓ 34%; rifabutin AUC ↓ 19%.	Co-administration should be avoided. If used, monitor for therapeutic response.
	Boceprevir	↑ in rifabutin concentrations are anticipated, while exposure of boceprevir may be ↓	Co-administration should be avoided, if possible. If used in combination, consider monitoring rifabutin concentration and adjust dose accordingly.
	Clarithromycin	Clarithromycin AUC ↓ 44%; rifabutin AUC ↑ 76%–99%.	Consider reducing rifabutin dose, monitor for rifabutin-associated toxicities, Consider monitoring serum concentration and adjust dose accordingly; or switch to azithromycin.
	Efavirenz	Rifabutin AUC ↓ 38%; no change in efavirenz exposure.	Increase rifabutin dose to 450–600 mg/day; effect of efavirenz + PI(s) on rifabutin concentrations has not been studied.
	Elvitegravir/cobicistat/ tenofovir/emtricitabine	Elvitegravir AUC ↓ 21%, C_{min} ↓ 67%; rifabutin active metabolite (25-O-desacetyl rifabutin) AUC ↑ 625%	Co-administration should be avoided, if possible. Consider using alternative antimycobacterial agent or alternative ARV drug. If used, consider rifabutin 150 mg once daily or every other day, consider monitoring rifabutin concentrations and adjust dose accordingly.
	Etravirine	Etravirine C_{min} ↓ 35% and AUC ↓ 37%; rifabutin AUC ↓ 17%.	Use standard rifabutin dose of 300 mg daily if not used with a ritonavir-boosted PI. In patients receiving a ritonavir-boosted PI, consider alternative agents if possible, or use serum concentration to guide dosing of rifabutin.
	Fluconazole	Rifabutin AUC ↑ 80%; no effect on fluconazole exposure.	Monitor for rifabutin toxicity and consider monitoring rifabutin concentrations and adjust dose accordingly; may need to reduce rifabutin dose to 150 mg/day.
	Itraconazole	Itraconazole AUC ↓ 70%; potential for ↑ rifabutin exposure.	Co-administration should be avoided, if possible. If the combination is to be used, monitor itraconazole and rifabutin concentrations and adjust doses accordingly. Monitor for rifabutin-associated toxicities.

Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 10 of 14)

Drug	Interacting With	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Rifabutin, continued	Maraviroc	Concentration of maraviroc may be ↓	If used without another strong CYP3A4 inducer or inhibitor, maraviroc 300 mg BID. If used with a strong CYP3A4 inhibitor, use maraviroc 150 mg BID.
	Nevirapine	Rifabutin AUC ↑ 17%, 25-O-desacetyl rifabutin AUC ↑ 24%; nevirapine C_{min} ↓ 16%.	No dose adjustment necessary.
	PI boosted by ritonavir	Significant ↑ in rifabutin concentrations.	Use rifabutin 150 mg daily or 300 mg 3 times/week. Consider monitoring rifabutin concentrations and adjust dose accordingly.
	Posaconazole	Posaconazole AUC ↓ 49%; rifabutin AUC ↑ 72%.	Co-administration should be avoided, if possible, or monitor posaconazole and rifabutin concentrations and adjust doses accordingly; monitor clinical response.
	Rilpivirine	Rilpivirine AUC ↓ 46%	Co-administration should be avoided.
	Telaprevir	Concentrations of telaprevir may be ↓, while rifabutin concentrations may be ↑	Co-administration should be avoided.
	Voriconazole	Voriconazole AUC ↓ 79%; rifabutin AUC ↑ 3-fold.	Co-administration should be avoided, if possible. If used in combination, monitor voriconazole and rifabutin concentrations and adjust dose accordingly. Monitor for clinical responses and toxicities.
Rifampin	Artemether/ lumefantrine	Artemether AUC ↓ 89%; DHA AUC ↓ 85%; lumefantrine AUC ↓ 68%	Co-administration should be avoided.
	Atovaquone	Atovaquone concentrations ↓ 52%; rifampin concentrations ↑ 37%	Co-administration should be avoided.
	Boceprevir	No PK data. Significant ↓ in boceprevir exposure is anticipated.	Co-administration should be avoided.
	Caspofungin	Caspofungin C_{min} ↓ 30%	Caspofungin dose should be increased to 70 mg/day.
	Clarithromycin	Mean clarithromycin concentrations ↓ 87%	This combination should be avoided; consider switching to azithromycin.
	Dapsone	Dapsone concentrations ↓ 7- to 10-fold and half-life ($t_{1/2}$) ↓ from 24 to 11 hours.	Co-administration should be avoided if possible. Consider alternatives for dapsone or use rifabutin.
	Doxycycline	Doxycycline AUC ↓ by 59%	Potential for decreased doxycycline efficacy; monitor closely for therapeutic failure.

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Drug	Interacting With	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Rifampin, continued	Efavirenz	Efavirenz AUC ↓ 22%, C_{min} ↓ 25%; no change in rifampin exposure.	Maintain efavirenz dose at 600 mg once daily and monitor for virologic response. Some clinicians suggest increasing efavirenz dose to 800 mg per day in patients >60 kg.
	Elvitegravir/cobicistat/ tenofovir/emtricitabine	Cobicistat and elvitegravir concentrations may be significantly ↓	Co-administration should be avoided. Consider an alternative antimycobacterial agent or alternative antiretroviral drug regimen.
	Etravirine	Potential significant ↓ in etravirine concentration.	Co-administration should be avoided.
	Fluconazole	Fluconazole AUC ↓ by 23%–56%; no change in rifampin exposure.	Monitor for antifungal efficacy, may need to increase fluconazole dose.
	Itraconazole	Itraconazole AUC ↓ 64%–88%; no change in rifampin concentrations.	Co-administration should be avoided. Consider alternative antifungal and/or antimycobacterial agent(s).
	Maraviroc	Maraviroc AUC ↓ 63%, C_{min} decreased 67%	Increase maraviroc dose to 600 mg twice daily or use alternative antimycobacterial agent.
	Nevirapine	Nevirapine AUC ↓ by >50%, C_{min} ↓ 21-37%; no change in rifampin concentrations.	This combination should be avoided if possible. If adding nevirapine to rifampin is necessary, initiate nevirapine at 200 mg twice daily (i.e., no lead-in period). Do not use nevirapine extended-release formulation.
	Posaconazole	Posaconazole concentrations may be ↓ significantly.	Co-administration should be avoided if possible. If used, monitor posaconazole concentrations and adjust dose if necessary.
	PI (+/- ritonavir-boosting)	Significantly ↓ PI exposure (>75%) despite ritonavir boosting	Co-administration should be avoided.
	Raltegravir	Raltegravir AUC ↓ 40%, C_{min} ↓ 60%	Increase raltegravir dose to 800 mg PO twice daily, monitor for antiretroviral efficacy, or switch to rifabutin.
	Rilpivirine	Rilpivirine AUC ↓ 80%	Co-administration should be avoided.
	Telaprevir	Telaprevir AUC ↓ 92%	Co-administration should be avoided.
	Voriconazole	Voriconazole AUC ↓ 96%	Co-administration should be avoided.
	Zidovudine	Zidovudine AUC ↓ 48%	Monitor for zidovudine efficacy.

Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 12 of 14)

Drug	Interacting With	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Telaprevir	Atazanavir/ritonavir	Telaprevir AUC ↓ 20%, C_{min} ↓ 15%; atazanavir C_{min} ↑ 85%	No dosage adjustment necessary.
	Clarithromycin	Concentrations of telaprevir and clarithromycin may be ↑ during co-administration.	Use with caution and monitor for adverse events, including QT prolongation. Reduce clarithromycin dose during concomitant use with telaprevir in patients with impaired renal function. Consider switching to azithromycin.
	Darunavir/ritonavir	Telaprevir AUC ↓ 35%, C_{min} ↓ 32%; darunavir AUC and C_{min} ↓ 40%.	Co-administration should be avoided.
	Efavirenz	Telaprevir AUC ↓ 26%; C_{min} ↓ 47%	Increase telaprevir dose to 1125 mg every 8 hours.
	Elvitegravir/cobicistat/ tenofovir/emtricitabine	No data. Potential for bi-directional interactions.	Co-administration should be avoided.
	Erythromycin	Concentrations of telaprevir and erythromycin may be ↑ during co-administration.	Use with caution and monitor for adverse events, including QT prolongation.
	Fosamprenavir/ ritonavir	Telaprevir AUC ↓ 32%, C_{min} ↓ 30%; amprenavir AUC ↓ 47%, C_{min} ↓ 56%	Co-administration should be avoided.
	Itraconazole	Concentrations of itraconazole and telaprevir may be ↑	If co-administration is necessary, high doses of itraconazole (>200 mg/day) are not recommended. Monitor for toxicities to both drugs. Consider monitoring itraconazole concentration and adjust dose accordingly.
	Lopinavir/ritonavir	Telaprevir AUC ↓ 54%, C_{min} ↓ 52%	Co-administration should be avoided.
	Posaconazole	Concentrations of posaconazole and telaprevir may be ↑	Use with caution and monitor for posaconazole-associated toxicities, including QT prolongation. Consider monitoring posaconazole concentration and adjust dose accordingly.
	Rifabutin	Concentrations of telaprevir may be ↑, while rifabutin concentrations may be ↑	Co-administration should be avoided
	Rifampin	Telaprevir AUC ↓ 92%	Co-administration should be avoided
	Tenofovir	Tenofovir C_{max}, AUC, and C_{min} ↑ 30%–41%	Monitor for tenofovir-associated toxicities.

Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 13 of 14)

Drug	Interacting With	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Telaprevir, continued	Voriconazole	Potential interaction; magnitude and direction unknown.	Co-administration should be avoided unless benefit is considered to outweigh risks; monitor for voriconazole-associated toxicities, including QT prolongation. Consider monitoring voriconazole concentration and adjust dose accordingly.
Tenofovir	Acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir	Potential for competitive active tubular secretion with these antiviral drugs.	Monitor for efficacy and toxicities of the antiviral agents and tenofovir.
	Atazanavir	Atazanavir AUC ↓ 25%, C_{min} ↓ 40%; tenofovir AUC ↑ 24%.	Atazanavir dose should be 300 mg daily given with ritonavir 100 mg daily when co-administered with tenofovir; monitor for tenofovir-associated toxicities.
	Darunavir/ritonavir	Tenofovir AUC ↑ 22%, C_{min} ↑ 37%	Monitor for tenofovir-associated toxicities.
	Didanosine	Didanosine AUC and C_{max} ↑ 48%–60%	Co-administration should be avoided. If co-administered, didanosine dose should be decreased to 250 mg once daily.
	Lopinavir/ritonavir	Tenofovir AUC ↑ 34%	Monitor for tenofovir-associated toxicities.
	Telaprevir	Tenofovir C_{max}, AUC and C_{min} ↑ 30–41%	Monitor for tenofovir-associated toxicities.
Voriconazole	Boceprevir	Concentrations of voriconazole may be ↑	Use with caution. Consider monitoring voriconazole concentration and adjust dose accordingly.
	Efavirenz	Voriconazole C_{max} ↓ 36–61%, AUC ↓ 55–77%; efavirenz C_{max} ↑ 38%, AUC ↑ 44%	Increase voriconazole maintenance dose to 400 mg q12h and decrease efavirenz to 300 mg daily. Consider monitoring voriconazole and/or efavirenz concentration and adjust doses accordingly.
	Elvitegravir/cobicistat/ tenofovir/emtricitabine	Voriconazole, elvitegravir, and cobicistat concentrations may be ↑	Monitor for voriconazole-associated toxicities. Consider monitoring voriconazole concentration and adjust dose accordingly.
	Etravirine	Voriconazole AUC ↑ 14%, C_{min} ↑ 23%; etravirine AUC ↑ 36%, C_{min} ↑ 52%	No dose adjustment necessary; monitor for etravirine-associated toxicities. Consider monitoring voriconazole concentration and adjust dose accordingly.

Table 5. Significant Pharmacokinetic Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (page 14 of 14)

Drug	Interacting With	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Voriconazole, continued	Nevirapine	Potential for ↓ voriconazole concentrations; however, no formal interaction data are available.	Monitor for therapeutic efficacy of voriconazole; consider monitoring voriconazole concentrations and adjust dose accordingly.
	PI boosted with ritonavir	Voriconazole AUC ↓ 39% (studied with ritonavir 100 mg BID). No interaction data for individual boosted PIs; however, potential for ↑ PI concentrations and ↓ voriconazole concentrations.	Consider monitoring voriconazole concentrations and adjust dose accordingly; monitor for PI-associated toxicities.
	Rifabutin	Voriconazole AUC ↓ 79%; rifabutin AUC ↑ 3-fold.	Co-administration should be avoided, if possible; if used in combination, monitor voriconazole and rifabutin concentrations, clinical responses, and toxicities from both drugs.
	Rifampin	Voriconazole AUC ↓ 96%	Co-administration should be avoided.
	Rilpivirine	No PK data. Possible ↑ rilpivirine concentration	Monitor efficacies and toxicities of both drugs. Consider monitoring voriconazole concentration and adjust dose accordingly.
	Telaprevir	Potential interaction; magnitude and direction unknown.	Co-administration should be avoided unless benefit is considered to outweigh risks; monitor for voriconazole-associated toxicities, including QT prolongation. Consider monitoring voriconazole concentration and adjust dose accordingly.

Key to Acronyms: ARV = antiretroviral; AUC = area under the curve; BID = twice daily = C_{max} = maximum concentration; C_{min} = minimum concentration; CrCl = creatinine clearance; CYP3A4 = Cytochrome P450 3A4; ddA-TP = dideoxyadenosine triphosphate; DHA = dihydroartemisinin; PI = protease inhibitor; PK = pharmacokinetic; TID = three times a day